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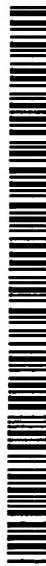
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WO 01/27129 A1

(54) Title: GLYCOSIDES AND ORTHOESTER GLYCOSIDES OF RALOXIFENE AND ANALOGUES AND THE USE THEREOF

(57) Abstract: Raloxifene and raloxifene analogue glycosides and orthoester glycosides afford greater serum bioavailability of the hydroxylated parent compound, and are useful for treating or preventing a number of conditions that may be treated with an anti-oestrogenic or an anti-androgenic compound.

GLYCOSIDES AND ORTHOESTER GLYCOSIDES OF RALOXIFENE AND ANALOGUES AND THE USE THEREOF

The present invention relates to derivatives of raloxifene and its analogues and the use thereof to treat conditions that are treatable with raloxifene and its analogues.

Raloxifene ([6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]
(4-[2-(1-piperidinyl)ethoxy]phenyl)methanone), its analogues and derivatives, have proven useful in treating a number of conditions. Among these are bone loss, hypercholesterolaemia and cancer (c.f. U.S. Patent Nos. 4,418,068, 5,393,763, 5,457,117, 5,478,847, 5,567,820, 5,641,790, 5,731,342, and 5,747,510).

US-A-5,563,054, entitled "Process for Preparation of Benzo[b]thiophene Glucuronides", describes a biotransformation process for the production of benzothiophene glucuronides from a benzothiophene (e.g., raloxifene) using *Streptomyces* sp. A93017. US-A-5,567,820, entitled "Glucopyranoside Benzothiophenes", describes the chemical synthesis of benzothiophene glucuronides.

U.S. Patent Nos. 5,972,383 and 5,811,120 disclose that a particularly useful salt of raloxifene is the hydrochloride. However, the aqueous solubility of raloxifene hydrochloride is poor, which somewhat limits its bioavailability. These patents teach that one can overcome the limited bioavailability of raloxifene hydrochloride by administering it as part of a pharmaceutical composition comprising a hydrophilic carrier composition.

US-A-5,612,317 discloses methods of treating and preventing osteoporosis and alleviating the symptoms of menopause by administering an oestrogen glycoside, or oestrogen orthoester glycoside.

US-A-5,508,392 discloses methods of treating and preventing osteoporosis by administering a vitamin D glycoside or vitamin D orthoester glycoside, or an analogue

WO 01/27129

PCT/GB00/03864

2

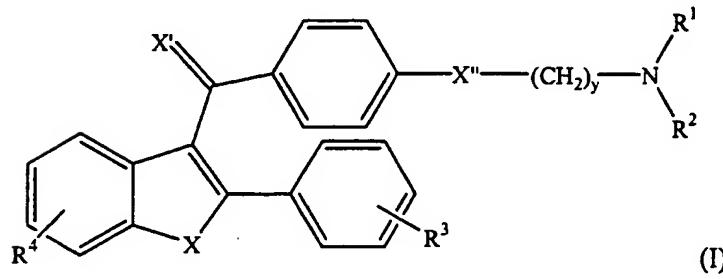
thereof.

More recently, raloxifene has been found to be useful in this area, but suffers because it has very low bioavailability.

Surprisingly, the glycosides and orthoester glycosides of raloxifene and its analogues provide higher bioavailability of the parent compound.

Thus, in a first aspect, the present invention provides glycosides and orthoester glycosides of raloxifene and analogues thereof.

In an alternative aspect, the present invention relates to a compound of Formula (I):



wherein:

X, X' and X" are each the same or different and are O or S;

y is an integer from 1 to 6, inclusive;

R¹ and R² are independently hydrogen, -C₁₋₇alkyl, -C₃₋₇cycloalkyl, -C₁₋₇alkyl-Y or phenyl, or, together, form a lower alkylene, a lower heteroalkylene, a lower alkenylene or lower heteroalkenylene group having from 3 to 6 atoms; and

Y is halogen, H, alkylcarbonyloxy, formyloxy or formyl;

R³ and R⁴ are the same or different and each represents H, halo, hydroxy, lower alkyl, lower hydroxyalkyl, lower haloalkyl or lower alkoxy group, or -OQ,

WO 01/27129

PCT/GB00/03864

3

wherein Q is a straight or branched chain glycosidic residue or glycosidic orthoester residue, or amino derivative thereof,
provided that at least one of the groups Q is a glycoside or orthoester glycoside or amino derivative thereof;
or a pharmaceutically acceptable salt or ester thereof.

The compounds of the invention exhibit higher plasma levels of the active, de-glycosylated compound than raloxifene administered alone. Thus, less of the compound needs be administered than with raloxifene alone, and it is easier to achieve useful levels of the parent compound in the serum.

Without being bound by theory, it is believed that the glycosides and orthoester glycosides of the present invention yield the active compound only after passing through the liver, unlike raloxifene, which suffer substantial first-pass degradation in the liver before reaching the general circulation.

Thus, the compounds of the present invention serve as protected precursors of the active raloxifene or analogue. The glycoside or orthoester glycoside group is cleaved *in situ* to yield the active compound. The glycoside grouping is cleaved before the raloxifene or analogue can be metabolised, thereby protecting the active compound from first pass metabolism in the liver and making it available in the general circulation.

The invention further provides a pharmaceutical composition comprising a compound of the present invention and a pharmaceutically acceptable carrier therefor.

There is further provided one or more compounds of the present invention for use in the treatment and/or prophylaxis of a condition susceptible of treatment by raloxifene, especially those indicated herein and below.

The invention also relates to a method for treating or preventing a condition

WO 01/27129

PCT/GB00/03864

4

selected from the group consisting of hypercholesterolaemia, bone loss, oestrogen dependent cancer, and androgen dependent cancer, comprising administering to an animal having said condition an effective amount of a compound of the present invention.

Further conditions treatable by compounds of the present invention include CNS disorders, such as Alzheimer's and schizophrenia.

The present invention is a significant advance in the art, as the bioavailability of the glycosides and orthoester glycosides of raloxifene and its analogues can be greatly improved relative to raloxifene and its salts. The active compounds are released in the body, e.g. the liver, where the glycosides and ortho ester glycosides are cleaved. The increased bioavailability of the glycosides and orthoester glycosides of raloxifene require a lower dosage of the drug to be administered. Moreover, the glycosides and orthoester glycosides can be more easily formulated due to their greater hydrophilicity.

The preferred route of administration is *per os*.

As provided herein, the term "alkyl", alone or in combination, refers to a straight or branched chain, saturated, hydrocarbon group having from 1 to 7 carbon atoms, unless otherwise indicated. The term "lower alkyl" is used herein to indicate an alkyl group having from 1 to 4 carbon atoms, unless otherwise indicated. Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, isobutyl, t-butyl, n-pentyl, 2-methylpentyl, n-hexyl, 4-methylhexyl, 3-ethylpentyl, and n-heptyl.

The term "haloalkyl" is defined herein as an alkyl group having one or more halo substituents. The halo substituents are preferably chosen from fluorine, chlorine, bromine and iodine.

The term "alkoxy" refers to the group "alkyl-O-", wherein "alkyl" includes any of the C₁ to C₄ alkyl groups mentioned above, which includes by way of example methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, t-butoxy and the like.

The term "cycloalkyl" is defined herein to include cyclic hydrocarbon radicals having from 3 to 7 ring carbon atoms. Some exemplary cycloalkyl radicals include the cyclopropyl, cyclobutyl, cyclobutyl, and cyclopentyl groups. A preferred cycloalkyl group is cyclohexyl.

The term "aryl," alone or in combination, is defined herein as a wholly unsaturated, optionally substituted, monocyclic or polycyclic group, having from 6 to 14 carbon atoms, preferably a monocyclic or bicyclic group, *e.g.*, phenyl or naphthyl. Substituted aryl groups may be substituted, for example, with one or more and, in particular, one to three, substituents selected from halogen, alkyl, hydroxy, alkoxy, haloalkyl, nitro, amino, acylamino, alkanoyl, alkylthio, alkylsulphanyl and alkylsulphonyl groups. Some exemplary aryl groups include phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-iodophenyl, 2-methylphenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3-trifluoromethylphenyl, 4-nitrophenyl, 3-acetoxyphenyl, 4-acetylaminophenyl, 2-methylthiophenyl, 8-hydroxynaphthyl, 6-isopropynaphthyl, and the like.

The term "aralkyl" refers to the group "-alkylaryl," wherein "alkyl" includes any of the C₁ to C₄ alkyl groups mentioned above and "aryl" includes any of the monocyclic or polycyclic aromatic groups mentioned above.

The term "heteroaryl" is defined herein as for aryl above, but containing one or more heteroatoms in place of one or more carbon atoms. Typically, the heterocycle will be 5- or 6- membered ring containing one, two or three, preferably one or two, heteroatoms, to which a carbocyclic, especially monocyclic aryl, group may be attached. The heterocyclic, aromatic group, or heteroaryl, optionally carrying a fused benzene ring, for example, may optionally be substituted. Preferred substituents are selected from halogen, alkyl, hydroxy, alkoxy, haloalkyl, nitro, amino, acylamino, alkylthio, alkylsulphanyl and alkylsulphonyl. There may be one or more substituents and, in particular, one to three substituents.

WO 01/27129

PCT/GB00/03864

The term "halogen" is defined herein to include fluorine, chlorine, bromine and iodine.

The term "linear and cyclic heteroalkyl" are defined in accordance with the term "alkyl" with the suitable replacement of carbon atoms with a heteroatom, such as nitrogen, oxygen or sulphur, in a manner sufficient to render a chemically stable species.

In general, it is preferred that X represents a sulphur atom, so that the core bicyclic structure is a benzothiophene.

X' and X" may be the same or different, but it is preferred that both represent oxygen atoms.

The integer y is suitably 1, 2, 3 or 4, with the group -(CH₂)_y preferably being ethylene or propylene, especially ethylene.

When R¹ and R² are C₁₋₄ alkyl, then it is preferred that they are either methyl or ethyl, and it is preferred that they are the same.

When R¹ and R², together with the nitrogen atom to which they are attached, form a heterocyclic ring, then it is preferred that this be selected from piperidinyl, pyrrolidinyl, morpholinyl, and 1-hexamethyleneiminy, especially piperidinyl and pyrrolidinyl, particularly piperidinyl.

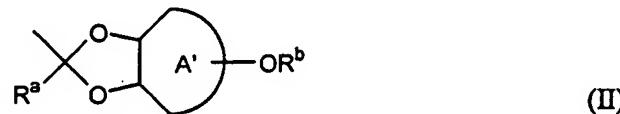
When one of R³ and R⁴ represents a group other than a glycoside, then it is preferred that this group is H, methyl or iodo, especially hydrogen.

When Q is a glycosidic residue, then it is preferred that it contain 1-20 glycosidic units. When Q is a glycosidic orthoester residue, then it is preferred that it have the Formula (II):

WO 01/27129

PCT/GB00/03864

7



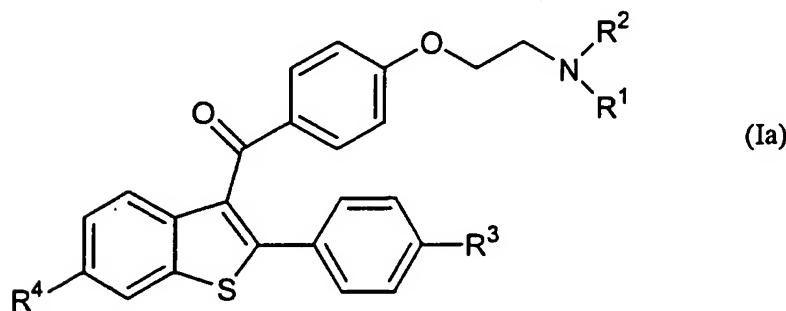
wherein A' represents a glycofuranosyl or glycopyranosyl ring or amino derivative thereof;

R^a is hydrogen, lower C₁₋₄ alkyl, C₇₋₁₀ aralkyl, phenyl; or phenyl substituted by chloro, fluoro, bromo, iodo, lower C₁₋₄ alkyl or lower C₁₋₄ alkoxy; or naphthyl; and R^b is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue.

In general, it is preferred that at least one group Q is a glucopyranoside residue.

In preferred compounds, R¹ and R², together with the nitrogen atom to which they are attached, form a heterocyclic ring.

A preferred group of compounds is those of Formula (Ia):



wherein R¹ and R² are the same or different and are C₁₋₄ alkyl or R¹ and R², together with the nitrogen atom to which they are attached, form a heterocyclic ring selected from the group consisting of piperidinyl, pyrrolidinyl, morpholino, or 1-hexamethyleneimino;

R³ and R⁴ are the same or different and are -OQ, wherein Q is hydrogen or a straight or branched chain glycosidic residue, or amino derivative thereof, containing 1-20 glycosidic units per residue, an orthoester glycoside moiety of the Formula (II);

WO 01/27129

PCT/GB00/03864

and pharmaceutically acceptable salts and esters thereof.

Especially preferred compounds of Formula (I) include, individually, and without limitation:

6-(1'-O- β -glucopyranosyl)-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)-benzoyl]benzo[b]thiophene;

6-hydroxy-2-(4-(1'-O- β -glucopyranosyl)phenyl)-3-[4-(2-piperidinoethoxy)-benzoyl]benzo[b]thiophene; and

6-(1'-O- β -glucopyranosyl)-2-(4-(1'-O- β -glucopyranosyl)phenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene;

and the pharmaceutically acceptable salts and esters thereof.

It will be appreciated that, while the present invention extends to all compounds of formula (I) and salts and esters thereof, those compounds formulated for pharmaceutical use should be pharmaceutically acceptable, as formulated. Compounds which do not fall into this category may be employed in the synthesis of compounds which do, for example.

The compounds of the present invention may be used according to well known methods of using raloxifene and derivatives thereof, *e.g.* for use in treating conditions characterised by bone loss (*e.g.*, post-menopausal osteoporosis, ovariectomy patients, senile osteoporosis, patients undergoing long-term treatment of corticosteroids, side effects from glucocorticoid or steroid treatment, patients suffering from Cushing's syndrome, gonadal dysgenesis, periarticular erosions in rheumatoid arthritis, osteoarthritis, Paget's disease, osteohalisteresis, osteomalacia, hypercalcaemia of malignancy, osteopenia due to bone metastases, periodontal disease, and hyperparathyroidism), hypercholesterolaemia, androgen and oestrogen dependent cancers (*e.g.*, prostatic, uterine and breast cancer) and other conditions (See U.S. Pat. Nos. 4,418,068, 5,393,763, 5,457,117, 5,478,847, 5,567,820, 5,641,790, 5,731,342, and 5,747,510). The compounds may also be used prophylactically to prevent the conditions enumerated above.

WO 01/27129

PCT/GB00/03864

9

The compounds useful in the practice of the invention may contain at least one glycoside or orthoester glycoside residue on the A ring of the compound of Formula II. The glycoside can typically comprise up to 20 glycosidic units. Preferred, however, are those having less than 10, most preferred, those having 3 or less glycosidic units. Specific examples are those containing 1 or 2 glycosidic units in the glycoside residue.

By glycosidic units are meant glycopyranosyl or glycofuranosyl, as well as their amino sugar derivatives. The residues may be homopolymers, random or alternating polymers, or block copolymers of these monomers. The glycosidic units have free hydroxy groups, or the hydroxy groups may be acylated, *e.g.* with a group $R^5-(C=O)-$, wherein R^5 is hydrogen, lower C₁₋₆ alkyl, C₆₋₁₀ substituted or unsubstituted aryl or C₇₋₁₆ aralkyl. Preferably, the acyl groups are acetyl or propionyl. Other preferred R^5 groups are phenyl, nitrophenyl, halophenyl, lower alkyl substituted phenyl, lower alkoxy substituted phenyl and the like or benzyl, lower alkoxy substituted benzyl and the like.

The glycopyranose or glycofuranose ring or amino derivative thereof may be fully or partially acylated or completely deacylated. The completely or partially acylated glycoside is useful as a defined intermediate for the synthesis of the deacylated material.

Among the possible glycopyranosyl structures are glucose, mannose, galactose, gulose, allose, altrose, idose, or talose. Among the furanosyl structures, the preferred ones are derived from fructose, arabinose or xylose. Among preferred diglycosides are sucrose, cellobiose, maltose, lactose, trehalose, gentiobiose, and melibiose. Among the triglycosides, the preferred ones may be raffinose or gentianose. The preferred amino derivatives are N-acetyl-D-galactosamine, N-acetyl-D-glucosamine, N-acetyl-D-mannosamine, N-acetylneuraminic acid, D-glucosamine, lyxosylamine, D-galactosamine, and the like.

When more than one glycosidic unit is present on a single hydroxy group, *i.e.*, di or polyglycosidic residues, the individual glycosidic rings may be bonded by 1-1, 1-2, 1-3, 1-4, 1-5 or 1-6 bonds, most preferably 1-2, 1-4 and 1-6. The linkages between individual

WO 01/27129

PCT/GB00/03864

10

glycosidic rings may be α or β .

Useful pharmaceutically acceptable salts include acid addition salts, *e.g.*, salts with inorganic acids such as HCl, HBr, sulphuric, sodium hydrogen sulphate, phosphoric acid, sodium dihydrogen phosphate, and disodium hydrogen phosphate, as well as salts with organic acids such as formic, acetic, benzoic, carbonic and the like. Where the compound is substituted by a carboxy group, pharmaceutically acceptable salts may be obtained with an inorganic base such as an alkali or alkaline earth metal hydroxide [*e.g.* LiOH, NaOH, KOH, or Ca(OH)₂] or an organic base such as choline hydroxide, spermidine, spermine, glucamine and the like.

The water soluble glycosidic derivatives of the aforementioned compounds may be obtained according to the general methods disclosed by Holick in U.S. Patent 4,410,515, the contents of which are fully incorporated by reference herein. The glycosyl orthoester compounds may be obtained according to U.S. Patent 4,521,410, the contents of which are fully incorporated by reference herein.

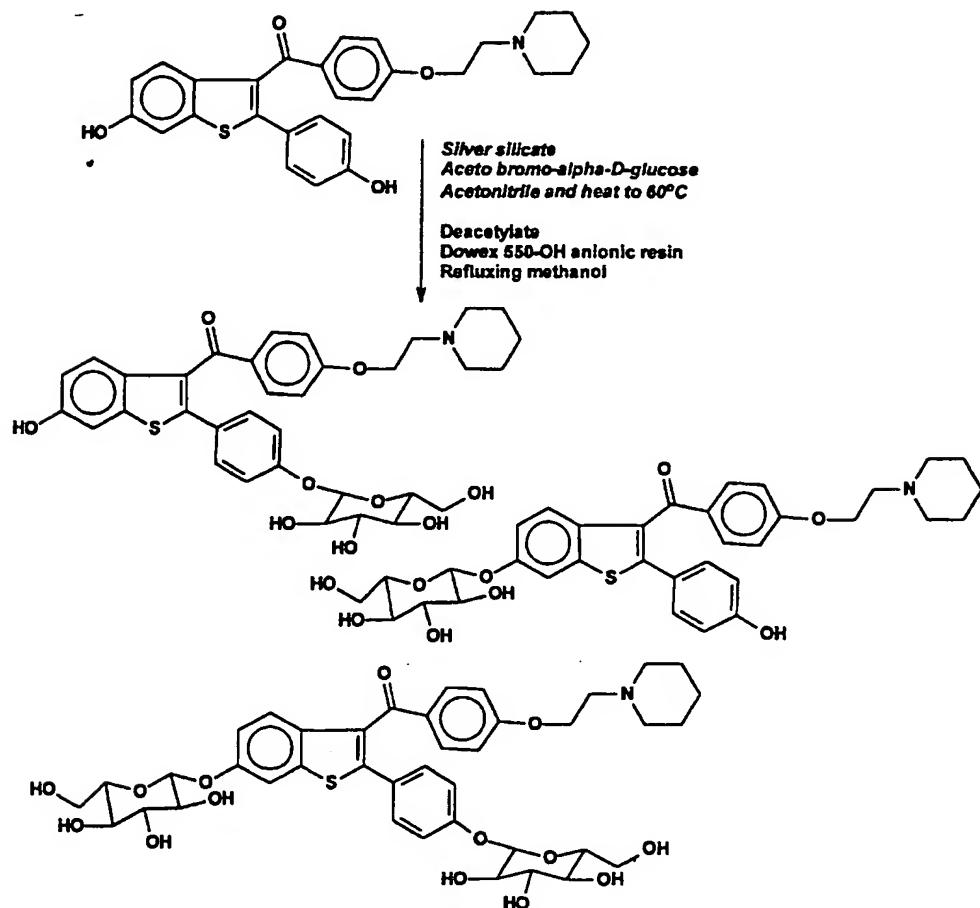
Scheme I presents a general method of preparing the glycosyl derivatives of raloxifene.

The mixture of compounds once made may then be separated by conventional methods including crystallisation, differential solubility in solvents, reversed phase HPLC, normal phase HPLC or column chromatography.

WO 01/27129

PCT/GB00/03864

11

Scheme I

Alternatively, the raloxifene mono-glycosides may be prepared using the mono-*t*-butyldimethylsilyl raloxifene derivatives described in US-A-5,567,820. Reaction of the mono-*t*-butyldimethylsilyl raloxifene with the glycosylating or orthoester glycosylating reagent according to U.S. Patent Nos. 4,410,515 and 4,521,410, followed by cleavage of the silyl ether with fluoride ion in methanol gives the mono-glycosyl and orthoester glycosyl raloxifene. The acyl groups may then be partially or fully removed to give the final product.

Any animal which may benefit from the compounds of Formula I, may be treated according to the present invention. Preferred animals are mammals, *e.g.* humans, although the invention is not intended to be so limited.

For oral administration, the compounds of the invention can be administered in any appropriate pharmaceutically acceptable carrier. The compounds of the invention may also be administered in any appropriate pharmaceutical carrier for parenteral, intramuscular, transdermal, intravenous, intranasal or inhalation administration. They can be administered by any means that achieve their intended purpose.

The dosage administered will depend on the age, health and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. An exemplary systemic daily dosage is about 0.05 mg/kg to about 100 mg/kg of body weight, more preferably, from about 0.1 to about 80 mg/kg of body weight, most preferably, about 1-10 mg/kg of body weight of the glycoside or orthoester glycoside, in one or more dosages per day, or a pharmaceutically acceptable salt thereof, is effective to obtain the desired results. In a preferred embodiment, the dosage is about 80 mg of raloxifene glucoside daily, although higher doses such as 100, 200 and 500 mg/daily may be given. In a more preferred embodiment, a low dose of raloxifene glycoside is administered, *e.g.* 1 mg, 5 mg, 10 mg, or 30 mg per day. One of ordinary skill in the art can determine the optimal dosages and concentrations of the glycoside and orthoester glycoside compounds of the invention with only routine experimentation.

WO 01/27129

PCT/GB00/03864

13

The compounds can be employed in dosage forms such as tablets, capsules or powder packets, or liquid solutions, suspensions or elixirs for oral administration, as well as sterile liquid for formulations such as solutions or suspensions for parenteral use. A lipid vehicle can be used in parenteral administration. The compounds may also be administered via topical patches, ointments, gels, liposomes or other transdermal applications. In such compositions, the active ingredient will ordinarily be present in an amount of at least 0.01% by weight based on the total weight of the composition, and not more than 90% by weight. An inert pharmaceutically acceptable carrier is preferable such as 95% ethanol, vegetable oils, propylene glycols, saline buffers, sesame oil, etc.

Reference is made to *Remington's Pharmaceutical Sciences*, 18th Edition, Gennaro *et al.* (eds.), 1990, for methods of preparing pharmaceutical compositions.

Topical formulations for transdermal, intranasal or inhalation administration may be prepared according to methods well known in the art. For topical administration, the compounds may be applied in any of the conventional pharmaceutical forms. For example, the compounds may be administered as part of a cream, lotion, aerosol, ointment, powder, liposomes or drops. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Such bases may include water and/or an oil such as liquid paraffin or a vegetable oil such as peanut oil or castor oil. Thickening agents which may be used include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, wool-fat, hydrogenated lanolin, beeswax and the like.

Lotions may be formulated with an aqueous or oily base and will in general also include one or more of a stabilising agent, thickening agent, dispersing agent, suspending agent, thickening agent, colouring agent, perfume and the like.

Powders may comprise any suitable powder base including talc, lactose, starch and the like. Drops may comprise an aqueous or non-aqueous base together with one or more dispersing agents, suspending agents, solubilising agents and the like.

WO 01/27129

PCT/GB00/03864

14

Preferred liposomes are NOVASOMES sold by IGI, Inc. (Buena, NJ) and described in U.S. Pat. No.5,260,065.

The compositions may further comprise one or more preservatives including bacteriostatic agents including methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chloride and the like.

The topical compositions comprise from about 0.0001% to 10% by weight, preferably, 0.001 to 0.5% by weight, more preferably, 0.01 to 0.25% by weight.

The compounds may be administered using, for example, pressurised metered-dose inhalers which deliver aerosolised particles suspended in chlorofluorocarbon propellants such as CFC-11, CFC-12 or the non-chlorofluorocarbons, HFC-134A or HFC-227, with or without surfactants and suitable bridging agents; dry powder inhalers which are either breath activated or delivered by air or gas pressure such as the dry powder inhaler disclosed in PCT/US92/05225; the TURBOHALERTM (Astra Pharmaceutical Products, Inc.) or ROTAHALERTM (Allen & Hamburys) which may be used to deliver the compounds as a finely milled powder in large aggregates either alone or in combination with some pharmaceutically acceptable carrier (e.g. lactose); and nebulisers. Reference is made to *Remington's Pharmaceutical Sciences*, 18th Edition, Gennaro *et al.* (eds.), 1990.

The compounds may also be administered in specific, measured amounts in the form of an aqueous solution or suspension by use of a pump spray bottle such as the bottles used to deliver VANCENASE AQTM Nasal Spray. The aqueous solution or suspension may be prepared by admixing the compound with water and other pharmaceutically acceptable carriers. See PCT/US91/06249. The aqueous suspensions may contain from about 0.001 to 100.0 mg, preferably, 0.1 to 10.0 mg of the compound per gram of suspension. The aqueous solution or suspension may comprise auxiliaries and/or one or more excipients such as suspending agents (e.g. microcrystalline cellulose, sodium carboxymethyl-cellulose, hydroxypropylmethyl cellulose), humectants (e.g. glycerine or propylene glycol), acids, bases or buffer substances for adjusting the pH (e.g. citric acid,

WO 01/27129

PCT/GB00/03864

15

sodium citrate, phosphoric acid, sodium phosphate as well as mixtures thereof); surfactants (e.g. polysorbate 80) and antimicrobial preservatives (e.g. benzalkonium chloride, phenethyl alcohol and potassium sorbate).

The compounds may be administered either individually or as a mixture containing non-glycosylated, monoglycosylated, and/or bisglycosylated compounds, or a mixture of the corresponding orthoester glycosides.

The compounds are preferably provided substantially pure prior to formulation. The phrase "substantially pure" encompasses compounds created by chemical synthesis and/or compounds substantially free of chemicals which may accompany the compounds in the natural state, as evidenced by thin layer chromatography (TLC) or high performance liquid chromatography (HPLC).

The present invention will now be further illustrated by reference to the following Examples, which are provided herein for purposes of illustration only and are not intended to be limiting unless otherwise specified.

Example 1

Isolation and Glucosylation of Raloxifene: Synthesis of a mixture of 6-(1'-O- β -2',3',4',6'-tetra-O-acetylglucopyranosyl)-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene; 6-hydroxy-2-(4-(1'-O- β -2',3',4',6'-tetra-O-acetylglucopyranosyl)phenyl)-3-[4-(2-piperidino-ethoxy)benzoyl]benzo[b]thiophene; and 6-(1'-O- β -2',3',4',6'-tetra-O-acetylglucopyranosyl)-2-(4-(1'-O- β -2',3',4',6'-tetra-O-acetylgluco-pyranosyl)phenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene

Isolation:

Raloxifene was isolated from 60 mg tablets from Eli Lilly. 200 tablets were ground and suspended in methanol (1 litre) and ground sodium bicarbonate (50 g) was added. The

WO 01/27129

PCT/GB00/03864

16

mixture was refluxed for 3 hours and filtered hot. Methanol was stripped and acetone (1 litre) was added. The mixture was refluxed and filtered hot. The crystals were collected. The filtrate was recycled to obtain a yellow powder which was homogeneous by TLC. 2 : 1 (v/v) dichloromethane : methanol, containing traces of triethylamine, was used as eluent.

The proton NMR spectrum of raloxifene was recorded in deuterated methanol:

δ 7.7 (d; Ar-H; 2 H);
 δ 7.4 (d; Ar-H; 2 H);
 δ 7.3 (s; Ar-H; 1 H);
 δ 7.2 (d; Ar-H; 2 H);
 δ 6.8 (multiplet; Ar-H; 3 H);
 δ 6.6 (d; Ar-H; 2 H);
 δ 4.18 (s; OCH₂);
 δ 2.75 (s; N-CH₂; 2 H);
 δ 2.55 (broad s; N-CH₂; 4 H);
 δ 1.7 and 1.5 (broad s; CH₂; 6 H).

Raloxifene (0.5 g) was suspended in dry acetonitrile (10 ml) and silver silicate (1.6 g; freshly prepared from silver fluoride and sodium metasilicate) was added. Molecular sieves (3 g) were added to the above mixture and the contents were stirred under argon for 20 minutes. To the above suspension was added acetobromo- α -D-glucose (1.0 g; 2 equivalents; freshly recrystallised from diethylether). The mixture was warmed to 60°C for 2 hours. The mixture was filtered through a bed of silica gel (100 g) and eluted with dichloromethane and methanol mixture (1 : 1 v/v, containing traces of triethylamine). The yellow eluent was concentrated under vacuum. The yellowish crystals weighed 580 mg. The product was less polar than the starting material by TLC.

Proton NMR spectrum was recorded in CDCl₃; the aromatic pattern was found to be different relative to raloxifene (δ 7.7 (d, 2 H); 7.6 (d, 1 H); 7.3 (m, 1 H); 7.15 (d, 2 H); 6.9 (d, 1 H); 6.7 (d, 2 H); and 6.6 (d, 2 H)). The sugar portion between δ 5.2 and 3.2 was,

WO 01/27129

PCT/GB00/03864

17

however, broadened due to association. The acetate signals at δ 2.0 were, however, very distinct. The spectrum was recorded as the free glucoside after the removal of insoluble sugar residues, if any, after the deacetylation using Dowex 550-AOH anionic resin.

Mass Spectral analysis.

M^+ ions (methanol) were obtained at 803.93 amu and 1134.2 amu (expected values for M^+ ions are 803.76 and 1134.2 for the 2 possible monoglucosides [*i.e.*, 6-(1'-O- β -2',3',4',6'-tetra-O-acetylglucopyranosyl)-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene and 6-hydroxy-2-(4-(1'-O- β -2',3',4',6'-tetra-O-acetylglucopyranosyl)phenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene) and one doubly glucosylated product (*i.e.*, 6-(1'-O- β -2',3',4',6'-tetra-O-acetylglucopyranosyl)-2-[4-(1'-O- β -2',3',4',6'-tetra-O-acetylglucopyranosyl)phenyl]-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene).

Example 2

**Deacetylation of the Mixture of Per-O-acetyl Glucopyranosides of Raloxifene:
Synthesis of**

6-(1'-O- β -glucopyranosyl)-2-(4-hydroxy-phenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene;
6-hydroxy-2-(4-(1'-O- β -glucopyranosyl)phenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene; and
6-(1'-O- β -glucopyranosyl)-2-(4-(1'-O- β -glucopyranosyl)phenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene

The yellowish crystals obtained above (0.5 g) were dissolved in hot methanol (30 ml), and Dowex-550 A-OH anion exchange resin (2 g) was added. The mixture was refluxed for 2 hours and filtered hot. The yellow filtrate, upon evaporation under vacuum, gave yellow crystals (340 mg). The product was found to be a mixture of glucosides by NMR spectrum. One attempt to effect HPLC separation of this mixture was unsuccessful. The mass spectrum indicated the presence of the glucoside as a mixture of mono and doubly glucosylated products. The product was, however, insoluble in methanol, unlike the starting material. Any free sugar residues were removed by extracting the product into ethyl acetate : triethyl amine mixture (5 : 1 v/v) and washing the organic portion with water.

WO 01/27129

PCT/GB00/03864

18

Mass spectrum: In methanol containing 1% formic acid M^+ ions at 636.6 (protonated glucoside as expected in theory at 636.7) and 798.8 (doubly glucosylated protonated molecular ion as expected in theory at 798.87).

UV spectrum in methanol: λ max at 291.8 and 248.8 nm with absorbance ratio of 1.97 : 1 similar to raloxifene at λ max at 288.9 and 249.2 with absorbance ratio of 2.5 : 1.

The proton NMR spectrum was complicated due to association in all the solvents tried. The product was soluble in deuterated dimethyl sulphoxide.

HPLC separation of Raloxifene glucosides:

Conditions: Waters delta 600 HPLC system with a dual UV detector from Waters 2487 and a manual injector was used for the separation.. Alltech-Phenyl column, 5 μ , 250mm length and ID 4.6mm; catalogue number # 88096 was connected. Solvent used for the elution was methanol at 1 ml/minute. UV monitoring of the peaks was done at 290nm.

Raloxifene glycoside mixture was dissolved in methanol and injected into the column. Three peaks were obtained @ 7.54, 9.28 & 11.98 minutes into the column. The peak at 11.98 minutes was the diglucoside and the two earlier peaks are the monoglucoside derivatives of raloxifene. The fractions at 7.54, 9.28 and 11.98 were confirmed as raloxifene derivatives by UV absorption spectrophotometry (λ_{max} 290 nm).

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions without undue experimentation. All patents, patent applications and publications cited herein are incorporated by reference in their entirety.

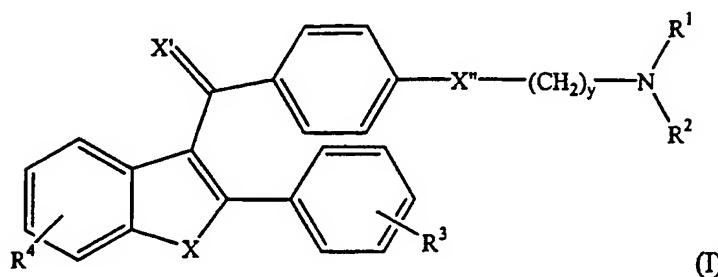
WO 01/27129

PCT/GB00/03864

19

Claims:

1. A compound of Formula (I):



wherein:

X, X' and X" are each the same or different and are O or S;

y is an integer from 1 to 6, inclusive;

R¹ and R² are independently hydrogen, -C₁₋₇alkyl, -C₃₋₇cycloalkyl, -O-C₁₋₇alkyl, -C₁₋₇alkyl-Y or phenyl, or, together, form a lower alkylene, a lower heteroalkylene, a lower alkenylene or lower heteroalkenylene group having from 3 to 6 atoms; and

Y is halogen, H, alkylcarbonyloxy, formyloxy or formyl;

R³ and R⁴ are the same or different and each represents H, halo, hydroxy, lower alkyl, lower hydroxyalkyl, lower haloalkyl or lower alkoxy group, or -OQ, wherein Q is a straight or branched chain glycosidic residue or glycosidic orthoester residue, or amino derivative thereof,

provided that at least one of the groups Q is a glycoside or orthoester glycoside or amino derivative thereof;

or a pharmaceutically acceptable salt or ester thereof.

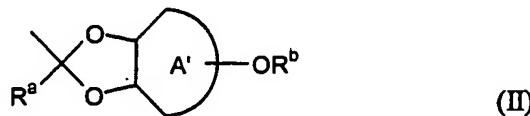
2. A compound according to claim 1, wherein X represents a sulphur atom.

WO 01/27129

PCT/GB00/03864

20

3. A compound according to claim 1 or 2, wherein X' and X" both represent oxygen atoms.
4. A compound according to any preceding claim, wherein the group -(CH₂)_y- represents an ethylene group.
5. A compound according to any of claims 1 to 3, wherein the group -(CH₂)_y- represents a propylene group.
6. A compound according to any preceding claim, wherein R¹ and R² are each either methyl or ethyl.
7. A compound according to any preceding claim, wherein R¹ and R² are the same.
8. A compound according to any preceding claim, wherein R¹ and R², together with the nitrogen atom to which they are attached, form a heterocyclic ring selected from piperidinyl, pyrrolidinyl, morpholinyl, and 1-hexamethyleneiminyl.
9. A compound according to claim 8, wherein the heterocyclic ring is piperidinyl.
10. A compound according to any preceding claim, wherein one of R³ and R⁴ represents a substituent other than a glycoside and is H, methyl or iodo.
11. A compound according to claim 10, and said substituent is hydrogen.
12. A compound according to any preceding claim, wherein each Q contains 1-2 glycosidic units.
13. A compound according to any preceding claim, wherein Q is a glycosidic orthoester residue having the Formula (II):



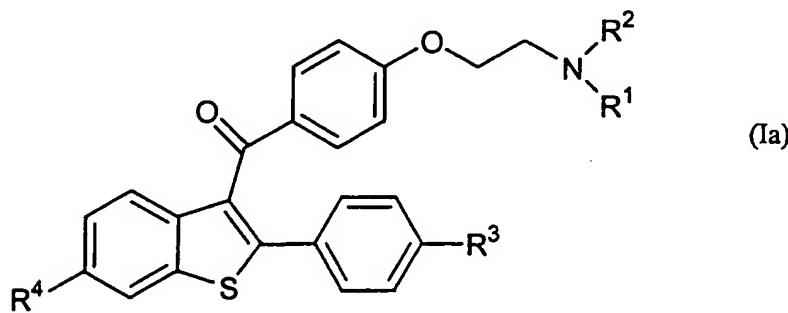
wherein A' represents a glycofuranosyl or glycopyranosyl ring or amino derivative thereof;

R^a is hydrogen, lower C₁₋₄ alkyl, C₇₋₁₀ aralkyl, phenyl; or phenyl substituted by chloro, fluoro, bromo, iodo, lower C₁₋₄ alkyl or lower C₁₋₄ alkoxy; or naphthyl; and R^b is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue.

14. A compound according to any preceding claim, wherein at least one group Q is a glucopyranoside residue.

15. A compound according to any preceding claim, wherein R¹ and R², together with the nitrogen atom to which they are attached, form a heterocyclic ring.

16. A compound according to any preceding claim, having the Formula (Ia):



wherein R¹ and R² are the same or different and are C₁₋₄ alkyl or R¹ and R², together with the nitrogen atom to which they are attached, form a heterocyclic ring selected from the group consisting of piperidinyl, pyrrolidinyl, morpholino, or 1-hexamethyleneimino;

R³ and R⁴ are the same or different and are -OQ, wherein Q is hydrogen or a straight or branched chain glycosidic residue, or amino derivative thereof, containing 1-20

WO 01/27129

PCT/GB00/03864

22

glycosidic units per residue, an orthoester glycoside moiety of the Formula (II);

and pharmaceutically acceptable salts and esters thereof.

17. A compound which is a glycoside or an orthoester glycoside, or amino derivative thereof, of raloxifene or of an analogue of raloxifene.

18. The compound of claim 1, wherein the glycosidic residues are at least partially acylated with a group $R^5-(C=O)-$, wherein R^5 is hydrogen, lower C_{1-6} alkyl, C_{6-10} substituted or unsubstituted aryl or C_{7-16} aralkyl.

19. The compound of claim 6, where R^5 is methyl.

20. 6-(1'-O- β -glucopyranosyl)-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene;
6-hydroxy-2-(4-(1'-O- β -glucopyranosyl)phenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene;
6-(1'-O- β -glucopyranosyl)-2-(4-(1'-O- β -glucopyranosyl)phenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene; or
a pharmaceutically acceptable salt or ester thereof.

21. A pharmaceutical composition comprising a compound according to any preceding claim together with a pharmaceutically acceptable carrier therefor.

22. A compound according to any of claims 1 to 20, for use in the treatment or prophylaxis of hypercholesterolaemia.

23. A compound according to any of claims 1 to 20, for use in the treatment or prophylaxis of bone loss.

24. A compound according to any of claims 1 to 20, for use in the treatment or

WO 01/27129

PCT/GB00/03864

23

prophylaxis of oestrogen dependent cancer.

25. A compound according to any of claims 1 to 20, for use in the treatment or prophylaxis of androgen dependent cancer.

26. A compound according to any of claims 1 to 20, for use in the treatment or prophylaxis of a CNS disorder selected from Alzheimer's and schizophrenia.

27. A compound according to any of claims 1 to 20, for use in the treatment or prophylaxis of endometrial cancer.

28. A compound according to any of claims 1 to 20, for use in the treatment or prophylaxis of breast cancer.

29. A compound according to any of claims 1 to 20, for use in the treatment or prophylaxis of prostatic cancer.

30. A compound according to any of claims 1 to 20, for use in the treatment or prophylaxis of bone loss resulting from post-menopausal osteoporosis.

31. Use of a compound according to any of claims 1 to 20, in the manufacture of a medicament for the treatment or prophylaxis of; hypercholesterolaemia, bone loss, oestrogen dependent cancer, androgen dependent cancer or a CNS disorder.

32. Use according to claim 31, wherein the medicament is adapted for oral administration.

INTERNATIONAL SEARCH REPORT

Inte	l Application No
PCT/GB 00/03864	

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	C07H15/26	A61K31/70	A61P35/00	A61P19/10	A61P25/00
	A61P25/28				

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7	C07H	A61K	A61P
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 567 820 A (DODGE JEFFREY A ET AL) 22 October 1996 (1996-10-22) cited in the application Y column 2-3 ---	1-5, 7-9, 12, 14-17, 21-32 1-32
Y	US 5 508 392 A (HOLICK MICHAEL F) 16 April 1996 (1996-04-16) the whole document ---	1-32
Y	WO 96 03995 A (HOLICK MICHAEL F) 15 February 1996 (1996-02-15) claims 1-10 ---	1-32 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

5 February 2001

Date of mailing of the international search report

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1

INTERNATIONAL SEARCH REPORT

Int. Jonal Application No
PCT/GB 00/03864

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DODGE J A ET AL: "Synthesis and estrogen receptor binding affinities of the major human metabolites of raloxifene (LY139481)" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 7, no. 8, 22 April 1997 (1997-04-22), pages 993-996, XP004136171 ISSN: 0960-894X the whole document —	1-5, 7-9, 12, 14-17, 21-32
X	EP 0 735 141 A (LILLY CO ELI) 2 October 1996 (1996-10-02) claims 1-9 & US 5 563 054 A 8 October 1996 (1996-10-08) cited in the application —	1-5, 7-9, 12, 14-17, 21-32
X	EP 0 683 170 A (LILLY CO ELI) 22 November 1995 (1995-11-22) the whole document —	1-5, 7-9, 12, 14-17, 21-32
A	WO 99 07693 A (BRYANT HENRY UHLMAN ; LILLY CO ELI (US); DODGE JEFFREY ALAN (US)) 18 February 1999 (1999-02-18) the whole document —	1, 21-32

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l. Application No.

PCT/GB 00/03864

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5567820	A 22-10-1996	AT 184880	T	15-10-1999
		AU 683734	B	20-11-1997
		AU 2012195	A	30-11-1995
		BR 9502079	A	05-03-1996
		CA 2149501	A	21-11-1995
		CN 1116626	A, B	14-02-1996
		CZ 9501262	A	13-12-1995
		DE 69512310	D	28-10-1999
		DE 69512310	T	03-02-2000
		DK 683170	T	20-12-1999
		EP 0683170	A	22-11-1995
		ES 2136799	T	01-12-1999
		FI 952420	A	21-11-1995
		GR 3032142	T	27-04-2000
		HU 73788	A	30-09-1996
		IL 113780	A	20-06-1999
		JP 7316180	A	05-12-1995
		NO 951954	A	21-11-1995
		NZ 272131	A	26-11-1996
		PL 308635	A	27-11-1995
		SI 683170	T	29-02-2000
		ZA 9503975	A	18-11-1996
US 5508392	A 16-04-1996	AU 5853894	A	19-07-1994
		CA 2152163	A	07-07-1994
		EP 0676951	A	18-10-1995
		JP 8505147	T	04-06-1996
		WO 9414411	A	07-07-1994
WO 9603995	A 15-02-1996	US 5612317	A	18-03-1997
		CA 2226140	A	15-02-1996
		EP 0894000	A	03-02-1999
EP 0735141	A 02-10-1996	US 5563054	A	08-10-1996
		CA 2173046	A	01-10-1996
		JP 8275795	A	22-10-1996
EP 0683170	A 22-11-1995	AT 184880	T	15-10-1999
		AU 683734	B	20-11-1997
		AU 2012195	A	30-11-1995
		BR 9502079	A	05-03-1996
		CA 2149501	A	21-11-1995
		CN 1116626	A, B	14-02-1996
		CZ 9501262	A	13-12-1995
		DE 69512310	D	28-10-1999
		DE 69512310	T	03-02-2000
		DK 683170	T	20-12-1999
		ES 2136799	T	01-12-1999
		FI 952420	A	21-11-1995
		GR 3032142	T	27-04-2000
		HU 73788	A	30-09-1996
		IL 113780	A	20-06-1999
		JP 7316180	A	05-12-1995
		NO 951954	A	21-11-1995
		NZ 272131	A	26-11-1996
		PL 308635	A	27-11-1995
		SI 683170	T	29-02-2000
		US 5567820	A	22-10-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/03864

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0683170 A		ZA	9503975 A	18-11-1996
WO 9907693 A	18-02-1999	AU	8824298 A	01-03-1999
		EP	0902025 A	17-03-1999